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A Facile Removal of the Arenesulfonyl Group by Electrochemical Reduction of Sulfonamides in a New Cooperative System of Anthracene and Ascorbic Acid: The Control of Crisscross Annulation

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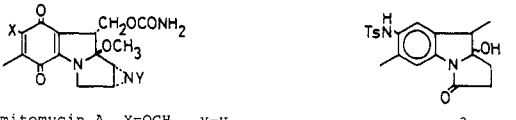
Electrochemical removal of the *N*-tosyl group from 2,5-bis[benzyl(*p*-tolylsulfonyl)amino]-4-(2,5-dioxo-1-methylcyclopentyl)toluene (**12**), which was easily derived from 2-amino-5-nitrotoluene through five steps in 94% overall yield, was successfully effected by a new cooperative system of anthracene and ascorbic acid, affording 1-benzyl-8-(benzylamino)-6,9-dimethyl-2,5-dioxo-1,2,3,4,5,6-hexahydro-1-benzazocine (**8**) through controlled crisscross annulation.

Although Kishi and co-workers[1] reported the first brilliant total synthesis of mitomycins in 1977, synthetic studies are still being intensively made by several groups,[2] and we also entered the difficult but attractive mitomycin area a few years ago,[3] in view of its unique structure and biological activity. In the past synthetic work, we have described the synthesis of 9a-hydroxy-5,8-dideoxymitosane (**1**) by the novel efficient method (Scheme I),[3] which has been generally applied to the synthesis of nitrogen-containing heterocycles, e.g., pyrrolizidines and indolizidines.[4]

In a general scheme of the new reaction, β-diketone **2** bearing the appropriate amino side chain is readily converted to **6** in a one-pot reaction under basic conditions through the formation of the amino ketone **4**, followed by a retroaldol type of ring opening to give **5**, and by transannular cyclization of **5** in the final step (Scheme II). This sequence of reactions is briefly depicted in formula **7** by a crisscross sign indicating variable σ-bonds and thereby called "crisscross annulation" as a trivial name.

If the keto lactam **5** were intercepted in this novel annulation, it would be possible to introduce various functional groups essential to a total synthesis of mitomycins. Therefore, we decided to synthesize the hydro-1-benzazocinone **8** as an important precursor for a synthetic strategy toward mitomycins (Scheme III). In this paper, we report a new facile electrochemical removal of an *N*-

Scheme I



mitomycin A, X=OCH_3, Y=H

mitomycin B[2]

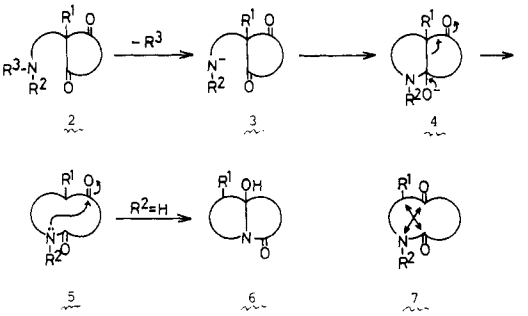
mitomycin C[2d] X=NH_2, Y=H

porfiromycin, X=NH_2, Y=CH_3

mitiromycin[2]

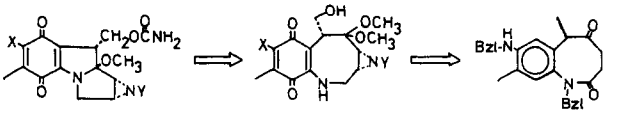
1[3]

Scheme II. Crisscross Annulation



2 **3** **4** **5** **6** **7**

Scheme III. Retrosynthesis of Mitomycins



mitomycins **8**

(1) (a) Nakatsubo, F.; Kocuzza, A. J.; Keeley, D. E.; Kishi, Y. *J. Am. Chem. Soc.* **1977**, *99*, 4835. (b) Nakatsubo, F.; Fukuyama, T.; Kocuzza, A. J.; Kishi, Y. *Ibid.* **1977**, *99*, 8115. (c) Fukuyama, T.; Nakatsubo, F.; Kocuzza, A. J.; Kishi, Y. *Tetrahedron Lett.* **1977**, 4295.

(2) (a) Nakano, K. *Heterocycles* **1979**, *13*, 373. (b) Kametani, T.; Takahashi, K. *Ibid.* **1978**, *9*, 293. (c) Takahashi, K.; Kametani, T. *Ibid.* **1979**, *13*, 411 and references cited therein. (d) Added in proof. Recently, the absolute configuration of mitomycin C was revised: Shirahata, K.; Hirayama, N. *J. Am. Chem. Soc.* **1983**, *105*, 7199.

(3) Ohnuma, T.; Sekine, Y.; Ban, Y. *Tetrahedron Lett.* **1979**, 2533, 2537.

(4) (a) Ohnuma, T.; Tabe, M.; Shiiya, K.; Date, T.; Ban, Y. *Tetrahedron Lett.* **1983**, *24*, 4249. (b) Ohnuma, T.; Nagasaki, M.; Tabe, M.; Ban, Y. *Ibid.* **1983**, *24*, 4253.

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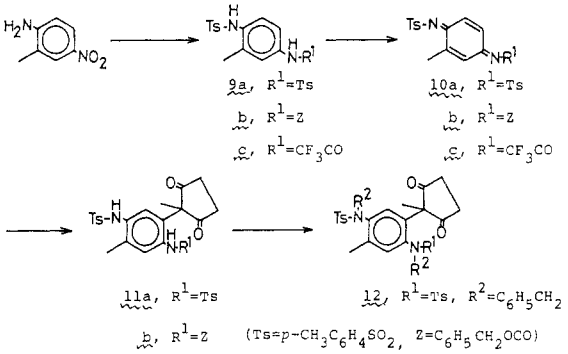
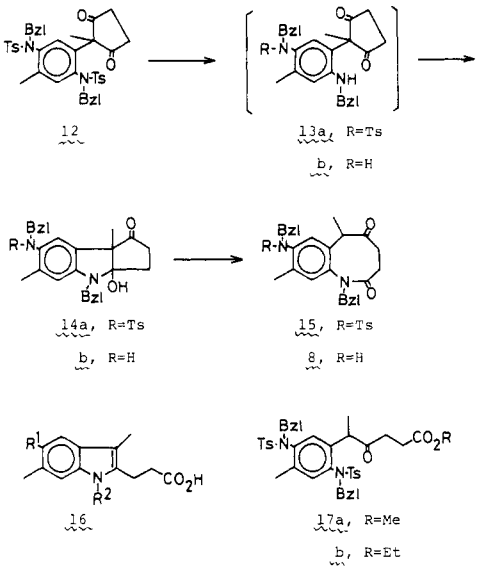
Scheme IV



Scheme V



tosyl protecting group with the combined assistance of anthracene and ascorbic acid and a one-pot synthesis of a strained medium-sized keto lactam **8**, usually not readily available,[5] by control of crisscross annulation.

Results and Discussion

The present synthetic approach involves a retroaldol type of ring-opening reaction of **4** as a key process to furnish the eight-membered ring system **5**, by interruption of the reaction sequence. We have already shown that the electron-withdrawing group was indispensable as an N-protecting group in order to accomplish readily the regiospecific Michael addition of **10** to **11** (Scheme IV).[3] It was also ascertained that annulation of **5** (R = H) to **6** was too fast to intercept the eight-membered ring system by any means.[3] Furthermore, it appeared that only the Michael adduct **11a** could be easily benzylated because of the inductive effect of the tosyl group; the benzyl group was to be later removed to form the secondary amine **3**. This sequence would enable the achievement of controlled crisscross annulation. Compound **12** was obtained easily from commercially available 2-amino-5-nitrotoluene in 94% overall yield. An attempt to oxidize the quinone diamide **9c** bearing the *N*-trifluoroacetyl protecting group by $Pb(OAc)_4$ failed to afford the corresponding quinone diimide **10c**, since it was very labile under these conditions. Moreover, the introduction of a benzyloxycarbonyl group (Z) made it very difficult to run the benzylation of Michael adduct **11b** essential to the production of the secondary amine.

Removal of the *N*-tosyl protecting group from *p*-toluenesulfonamides can be effected usually under rather drastic conditions.[6] For example, if deprotection of **12** was carried out at higher temperature in acidic medium, it can be predicted that indole-2-propionic acid **16** should be formed as a major product through the hydrolysis of amino ketone **14a** or **14b** generated after elimination of the tosyl group (Scheme V).[3]

An improved photochemical method was reported by Yonemitsu et al.[7] The improved reaction proceeds smoothly via intermolecular formation of the excited pair (exciplex) of electron-donating aromatic and electron-accepting sulfonamide. More remarkable is the important action of reductants, which shift equilibrium toward the products and control the course of photolysis through rapid reduction of the sulfinyl radical generated after cleavage of the sulfur–nitrogen bond.

Thus, the sulfonamide **12** was submitted to irradiation in aqueous THF containing 1,5-dimethoxynaphthalene (DMN) as an electron donor and ascorbic acid (Vc) as a reductant to afford **14b** in 48% isolated yield via the fast intramolecular cyclization of **13a** and/or **13b**. Unfortunately, the expected retroaldol type of ring-opening reaction, however, did not occur, since the photolysis had to be carried out under slightly acidic condition. As the ring-opening reaction generally proceeds under basic conditions,[3] the isolated compound **14b** was allowed to react then with NaH in THF at room temperature to afford **8** expectedly in 44% yield. Evidently, it is of great value as a synthetic method to produce a strained eight-membered ring system, if possible, in one pot (e.g., from **12** to **8**). Therefore, we have subsequently tried the electrochemical method.

In 1965, Horner and Neumann[8] discovered that the electrochemical reduction of simple sulfonamides at a mercury cathode in MeOH containing Me_4NCl as a supporting electrolyte led to the corresponding amines and toluenesulfinic acid in good yields. Later, the reaction mechanism and theory on the electrochemical removal of protecting groups have been appreciably elucidated by detailed study.[9] Thus, the method is now being used widely and easily as an attractive and useful preparative procedure. For example, by use of modified protecting groups (inner activation) or catalysts (so-called mediators or electron carriers, external activation), the electrolysis of sulfonamides can be run more smoothly under mild conditions.[9a]

At first, we conducted the controlled potential electrolysis of **12** using a lead cathode[10] in a DMF–MeOH (or

(5) In general, it is accompanied by a number of difficulties and multiple steps to afford medium-sized rings as shown in the following references: 2b; 2c; and Proctor, G. R.; Ross, W. I. *J. Chem. Soc., Perkin Trans. 1* **1972**, 885.

(6) (a) McOmie, J. F. W. "Protective Groups in Organic Chemistry"; Plenum Press: New York, 1973. (b) Greene, T. W. "Protective Groups in Organic Synthesis"; Wiley: New York, 1981.

(7) Hamada, T.; Nishida, A.; Matsumoto, Y.; Yonemitsu, O. *J. Am. Chem. Soc.* **1980**, *102*, 3978. They presented a part of this work at the 100th Annual Meeting of Pharmaceutical Society of Japan, April, 1980, and then they claimed that ascorbic acid also behaved as a useful reductant in the photolysis of N-tosylated peptides.

(8) Horner, L.; Neumann, H. *Chem. Ber.* **1965**, *98*, 3462.

(9) (a) Mairanovsky, V. G. *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 281 and references cited therein. It is also described that anthracene is one of the useful mediators for electrolysis of sulfonamides. (b) Benedetti, L.; Andreoli, R.; Gavioli, G. B.; Grandi, G. *J. Electroanal. Chem.* **1976**, *68*, 243. (c) Rastelli, A.; Andreoli, R.; Gavioli, G. B.; Grandi, G.; Benedetti, L. *Ibid.* **1978**, *89*, 207. (d) Andreoli, R.; Gavioli, G. B.; Grandi, G.; Benedetti, L.; Rastelli, A. *Ibid.* **1980**, *108*, 77. (e) Quartieri, S.; Benedetti, L.; Andreoli, R.; Rastelli, A. *Ibid.* **1981**, *122*, 247.

(10) (a) Okumura, K.; Iwasaki, T.; Matsuoka, M.; Matsumoto, K. *Chem. Ind. (London)* **1971**, 929. (b) Iwasaki, T.; Matsumoto, K.; Matsuoka, M.; Takahashi, T.; Okumura, K. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 852.

Table I. Effects of Additives for Electrolysis of Sulfonamide 12[a]

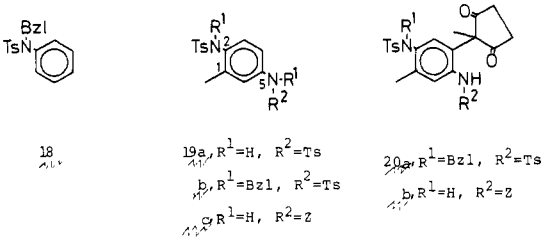
entry	anth,[b] m mol	additive, m mol	time, min	F/mol	products, % yield[c] 14a	8
1	0	0	10	1.9	9	2
2	0	0	23	3.6	0	0
3[d,e]	0	0	60	3.1	0	0
4[f]	0.1	0	8	1.3	32	7
5	0.1	0	20	3.5	0	0
6	0	Vc[g] (0.2)	37	4.9	2	41
7	0	AcOH (0.2)	38	5.0	1	22
8	0.1	*i*-PrOH (0.8)	36	5.5	0	2
9	0.1	Vc (0.1)	30	5.3	0	41
10	0.1	Vc (0.2)	40	6.6	0	68
11[h]	0.1	Vc (0.2)	44	5.3	0	61
12[d,i]	0.1	Vc (0.2)	8	1.5	21	0
13[d]	0.3	Vc (0.2)	26	5.0	11	48
14[d]	0.1	Vc (0.2)	34	7.1	0	58
15	0.1	Vc (0.3)	40	6.1	0	34
16	0.1	Vc (0.4)	60	7.7	0	19

[a] Sulfonamide **12** (0.1 mmol) was reduced at a mercury cathode in 7 mL of DMF/0.057 M Et_4NBF_4 at −2.00 V vs. Pt wire.[11] [b] Anth = anthracene. [c] Isolated yields. [d] Et_4NBr as a supporting electrolyte. [e] Used 85% aqueous DMF as a solvent. [f] Yielded **15** (9%). [g] Vc = ascorbic acid. [h] Carried out at −2.3 V vs. SCE. [i] Sulfonamide **12** was recovered (65%).

EtOH) solution containing a supporting electrolyte, e.g., Et_4NBF_4, Me_4NCl, Et_4NClO_4, *n*-Bu_4NI, or Et_4NOTs, at −1.7 to −2.2 V vs. Pt wire as a quasi-reference electrode.[11] Contrary to expectation, the alcoholysis of **12** proceeded preferentially to give **17a** or **17b** (40–63% yield) as major products. No reduction occurred at −2.2 to −2.5 V vs. Pt wire in DMF as a solvent. To solve this problem, we thoroughly investigated the electrochemical removal of the *N*-tosyl group using a mercury cathode in DMF and finally obtained successful results by utilizing a new system: the combined assistance of anthracene[9a] and ascorbic acid. The results are summarized in Table I. Several remarkable features of this method are discussed and described in detail as follows.

In the case of direct electrolysis of **12**, no desired compounds were isolated, which may be explained in two ways. First, the current distribution at the working electrode was not uniform; therefore the effective potential was not the same over the whole electrode.[12] Second, appropriate hydrogen sources could not be found in the neighborhood of the reaction species. In the first stage of the electrolysis, the removal of the *N*-tosyl group at C-5 proceeded rather easily with the assistance of anthracene alone as a mediator. Although it was reported[13] that the homogeneous electron transfer in solution from an anion radical ($A^{-\cdot}$) to a substrate was much easier than the heterogeneous one from an electrode, ascorbic acid was believed to be indispensable as an additional cofactor to complete the second stage of electrolysis at C-2 and finally to get a desired product. The addition of water or *i*-PrOH as a weak proton donor gave no favorable effects on the course of this reaction. The yield of **8** was improved to some extent by the addition of AcOH (22% yield) but much more by ascorbic acid (41% yield). Thus, the desired compound **8** was eventually obtained in one pot from **12**. Since the degrees of dissociation of acetic and ascorbic acids are almost equal, this notable effect seemed to involve important differences in reaction mechanism. It is even more notable that the yield of **8** was greatly improved to 68%

Scheme VI



by the combined assistance of ascorbic acid (2 mol equiv to **12**) and anthracene (1 mol equiv) and ultimately to 84% in the case of relatively large scale reactions.

Why did the electrolysis of **12**, contrary to the photolysis, proceed smoothyl to give the strained eight-membered keto lactam **8** in such high yields and in one pot from **12**?

In the case of electrochemical reduction, the proton seems to be practically excluded from the neighborhood of the reaction site (cathode). Furthermore, because of the presence of the anion radical of anthracene and/or triethylamine derived from the cleavage of the supporting electrolyte,[14] the electrochemical reduction of **12** actually appeared to be carried out in a rather basic medium. Working up the reaction mixture with water, the solution was usually observed to be at a pH slightly over 7, even when the electrolysis was done in the presence of an adequate amount of ascorbic acid. The choice of medium is also an important factor for the success of electrolysis. Carried out in an aprotic medium, where the dissociation of ascorbic acid is appropriately limited, anthracene could act effectively as a mediator; the naked anion generated from the electrolysis of **12** could participate in the successive ring-opening reaction prior to protonation by the acid. Even if protonated, the original naked anion could be regenerated again by the electrogenerated base (EGB^-),[15] i.e., the anion radical of anthracene and other anions derived from electrolysis of **12**. According to these reasons, the electrolysis of **12** successively proceeded to afford the desired compound **8** in one pot. The optimal

(11) (a) Lehmkuhl, H.; Leuchte, W.; Eisenbach, W. *Justus Liebigs Ann. Chem.* **1973**, 692. (b) Sawyer, D. T.; Roberts, J. L., *Jr.* "Experimental Electrochemistry for Chemists"; Wiley: New York, 1974.
(12) Simonet, J.; Lund, H. *Acta Chem. Scand., Ser. B* **1977**, *B31*, 909.
(13) Simonet, J.; Michel, M. A.; Lund, H. *Acta Chem. Scand., Ser. B* **1975**, *B29*, 489.
(14) (a) Yousefzadeh, P.; Mann, C. K. *J. Org. Chem.* **1968**, *33*, 2716. (b) Lund, H.; Michel, M.; Simonet, J. *Acta Chem. Scand., Ser. B* **1975**, *B29*, 217.
(15) (a) Shono, T.; Mitani, M. *J. Am. Chem. Soc.* **1968**, *90*, 2728. (b) Iversen, P. E.; Lund, H. *Tetrahedron Lett.* **1969**, 3523. (c) Baizer, M. M.; Chruma, J. L.; White, D. A. *Tetrahedron Lett.* **1973**, 5209.

Table II. Reduction Peak Potentials (Ep) derived from Cyclic Voltammograms[a]

entry	compd (c = 5 mM)	Ep (V vs. SCE)	
1	12	−2.08[b]	−2.28
2[c]	12	−2.32[b]	−2.51
3	14b	−2.7<	
4	8	−2.7<	
5	18	−2.15	
6	19a	−2.16	−2.27
7	19b	−2.20[b]	−2.30
8	19c	−2.20	−2.68
9	20a	−2.03	−2.19
10	20b	−2.21	−2.65
11	Anth[d]	−2.00	−2.55
12	Vc[e]	−2.24	
13	AcOH	−2.50[c]	

[a] Measured using a hanging mercury drop electrode[11b] in DMF/0.1 M Et_4NBF_4 at a sweep rate of 200 mV s^{-1}. [b] Appeared as shoulders. [c] Pt wire[11] was used as a quasi-reference electrode. [d] Anth = anthracene. [e] Vc = ascorbic acid.

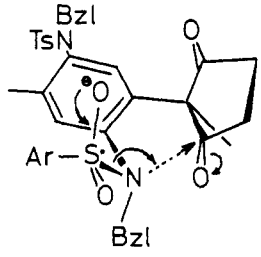


Figure 1. Transition state.

amount of ascorbic acid (2 mol equiv to **12**) is, therefore, essential to promote the reaction effectively.

To clarify the mechanism of this electrochemical reaction, cyclic voltammetry of **12**, the related sulfonamides, anthracene, and ascorbic acid was conducted by use of a hanging mercury drop electrode[11b] in DMF containing 0.1 M Et_4NBF_4 (Table II and Scheme VI).

The reduction peak potentials (Ep) of the TsNR (R = H, Bzl) substituent at the C-2 position of **19a** and **19b** are more negative than those of TsNR at C-5 (ΔEp = 0.10 V) in parallel with the Hammett relationship.[9] Note also that the Ep value of TsNR at C-5 in **12** is more positive than the corresponding one in **19b** (ΔEp = 0.12 V). The adsorption ability of each of the two sulfonamide groups in **12** should be almost equal at the surface of an electrode. Thus, this large difference could be ascribed to the electron-withdrawing inductive effect of the β-diketonyl group in **12** through a carbon atom[16] and/or a concerted mechanism with partial formation of a nitrogen–carbon bond in the transition state as shown in Figure 1. Therefore, the tosyl group at C-5 should be preferentially reduced to give the intermediate **14a** through a fast intramolecular cyclization reaction not followed by ring-opening reaction (except for entry 4 in Table I) because of the inductive effect of the *N*-tosyl group. That is, it is important for this ring opening to transfer the charge on the nitrogen atom through the carbon–carbon bond by attraction of the opposite carbonyl group (Scheme II). Different from keto *lactam* **15**, *amino ketone* **14b** *was usually detected in small* amounts by TLC in the course of reaction. Moreover, from the results of analysis of variable constituents in the course of reaction (entries 12–14 in Table I), this electrolysis of **12** appeared to proceed in a stepwise manner, **12** → **13a** → **14a** → **14b** → **8** (Scheme V).

Next, we measured the cyclic voltammetry of the mixed system to elucidate the role of anthracene and ascorbic acid in the electrolysis of **12** (Figures 2 and 3). As is well-

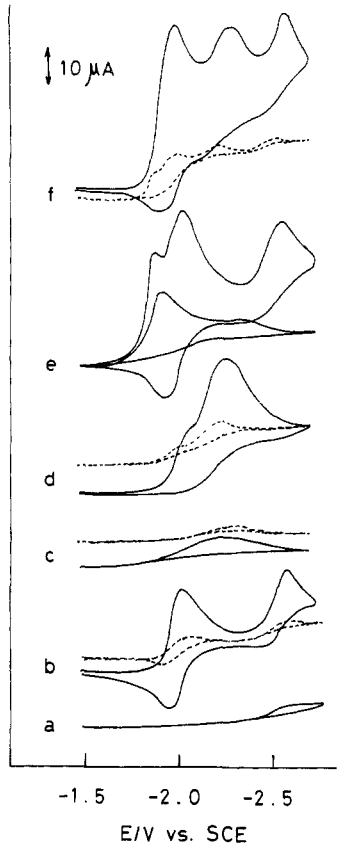


Figure 2. Cyclic voltammograms: (a) only 0.1 M Et_4NBF_4, (b) 5 mM anthracene, (c) 5 mM Vc, (d) 5 mM **12**, (e) 10 mM Vc + anthracene (5 and 10 mM), (f) 5 mM **12** + 5 mM anthracene. The solid and dashed curves demonstrate different sweep rates of 200 and 10 mV s^{-1}, respectively.

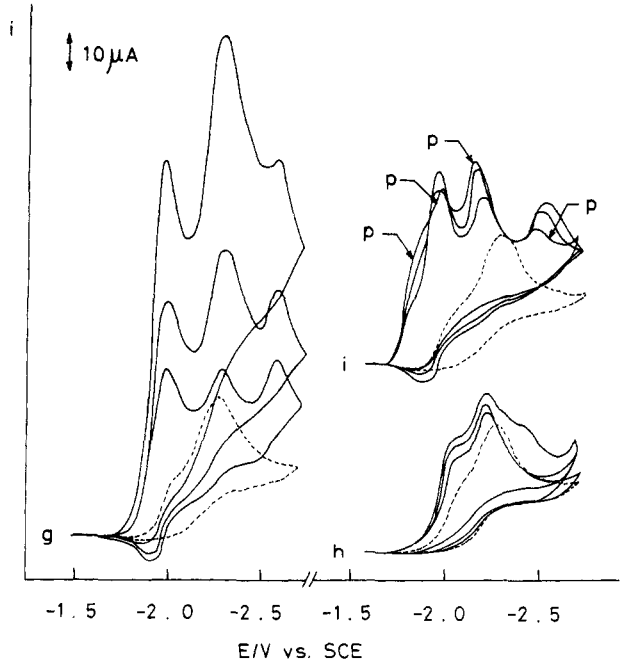
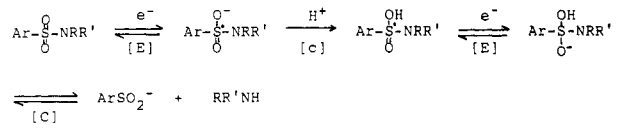


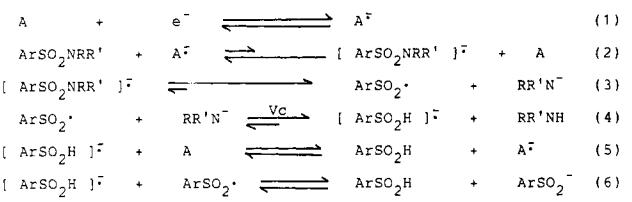
Figure 3. Cyclic voltammograms at a sweep rate 200 mV s^{-1}: (g) 5 mM anthracene + **12** (5, 10, and 20 mM), (h) 5 mM **12** + Vc (5, 10, and 15 mM), (i) 5 mM **12** + 5 mM anthracene + Vc (5, 10, and 15 (curve p) mM). The dashed curves demonstrate 5 mM **12**.

(16) Lambert, F. L. *J. Org. Chem.* **1966**, *31*, 4184.

Scheme VII



Scheme VIII



known,[9] anthracene (A) is reduced to the anion radical ($A^{-}\cdot$), indicating the first wave (Ep = −2.00 V), and successively to the dianion (A^{2-}), indicating the second wave (Ep = −2.55 V). The prewave[13,17] (Ep = −1.95 V, e) to the first wave (Ep = −2.00 V) of anthracene (A) was observed in the presence of ascorbic acid at a fast sweep rate (200 mV s^{-1}), which should be due to the cathodic reduction of monohydroanthracene radical (AH·) to the anion (AH^{-}). The radical (AH·) should have been formed by fast follow-up protonation of the anion radical ($A^{-}\cdot$) produced by electrolysis. This protonation of the anion radical ($A^{-}\cdot$) should unfavorably effect the catalytic electron transfer from that to **12** at sufficiently high concentration of ascorbic acid as shown in Table I. The whole process may be illustrated by ECEC mechanism:[17]

$$A \xrightarrow{e^{-}[E]} A^{-}\cdot \xrightarrow{H^{+}[C]} AH\cdot \xrightarrow{e^{-}[E]} AH^{-} \xrightarrow{H^{+}[C]} AH_2$$

A similar prewave (f) also appeared in the presence of **12**. It was also ascertained that the catalytic electron transfer actually proceeded from anthracene to **12** (g). It is noteworthy that addition of ascorbic acid shifted the reduction peak potential of **12** favorably to the more positive direction and also increased the cathodic peak currents (h). This significant effect by the addition of ascorbic acid was assumed to be due to the accerelation of the reduction of **12**, possibly by protonation[9a,17] of the anion radical in the ECEC mechanism as shown in Scheme VII. Externally, a similar behavior was also observed in the voltammetric experiments by the addition of AcOH, whereas the wave was entirely unaffected by the addition of *i*-PrOH (a weak proton donor). Though rather complicated, the advantageous features were also observed in the case of a mixed system of **12**, ascorbic acid, and anthracene (i).

Considering carefully the results of cyclic voltammetry and preparative photo- and electrochemical reaction, it seems reasonable to conclude that anthracene behaved as a mediator and that ascorbic acid acted as a proton donor and reductant to furnish the desired compound **8** in the electrolysis of **12**. Thus, this useful reaction could be explained on the basis of Scheme VIII.

Anthracene (A) is reduced to a stable anion radical (A·), by which the sulfonamide ($ArSO_2NRR'$) is reduced to an unstable and very short-lived radical having the unpaired electron localized at the sulfur atom.[14] It is also well-known that stages 2 and 3[18] are concerted within a collision complex[17] and that an arenesulfinyl radical in most but not all cases exchanges an electron with an anion radical ($A^{-}\cdot$, $[ArSO_2H]^{-}\cdot$, or $[ArSO_2NRR']^{-}\cdot$) and undergoes direct reduction at the electrode, dimerization, coupling, or hydrogen abstraction from a supporting electrolyte, substrate, and the converted species.[19] Therefore, in the case of electrolysis of rather complex sulfonamides, it seems most important to reduce immediately the sulfinyl radical generated in the course of electrolysis. Furthermore, an appropriate proton donor is also absolutely essential at the final stage to avoid the production of byproducts. Thus, the whole reaction sequence can be schematically illustrated by Scheme IX.

The present method developed by us could be considered as a new cooperative system, where ascorbic acid behaves as a proton donor and reductant in combination with anthracene and remarkably contributes to construction of the strained eight-membered ring system **8** by the controlled crisscross annulation. We are now striving toward the final goal, viz., the mitomycins themselves.

Experimental Section

Melting points were obtained on a Yamato MP-1 apparatus and were uncorrected. Infrared spectra were obtained on a JASCO IRA-2 spectrophotometer. ^1H NMR and ^{13}C NMR spectra were obtained on JEOL JNM-FX 100 (100 MHz) and JEOL JNM-FX 200 (200 MHz) spectrometers with Me_4Si as an internal standard. Mass spectra were obtained on a JEOL JMS-D 300 spectrometer. Elemental analyses were performed by the Center for Instrumental Analysis at our university. Controlled potential electrolyses were performed on a Yanaco VE8 potentiostat. Cyclic voltammograms were performed on a Nichia HP-E500H potentiostat equipped with an ES511 linear potential scanner and recorded on a Rikadenki RW-11 x-y recorder.

2,5-Bis[benzyl(*p*-tolylsulfonyl)amino]-4-(2,5-dioxo-1-methylcyclopentyl)toluene (12). To a mixture of 18.9 g (34.9 mmol) of **11a**[3] and 17.9 g (105 mmol) of benzyl bromide in 400 mL of acetone were added 14.5 g (105 mmol) of K_2CO_3 and 5.8 g (34.9 mmol) of KI, and the mixture was refluxed for 3 days. After cooling, the resulting precipitate was filtered and washed with acetone. The combined acetone extracts were removed under vacuum, and the residue was chromatographed on silica, eluting with $CHCl_3$. Crystallization from ether gave 24.7 g (98%) of **12** as colorless crystals: mp 189–190 °C; IR (Nujol) 1725, 1350, 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.11 (s, 2.3 H), 1.16 (s, 0.7 H), 1.55 (s, 2.3 H), 1.58 (s, 0.7 H), 2.28 (s, 2.3 H), 2.39 (s, 0.7 H), 2.45 (s, 2.3 H), 2.47 (s, 0.7 H), 2.7–3.6 (m, 4 H), 4.0–4.2 (m, 2 H), 4.74 (d, *J* = 14.7 Hz, 1 H), 4.99 (d, *J* = 12.2 Hz, 0.2 H), 5.19 (d, *J* = 12.2 Hz, 0.8 H), 5.31 (s, 0.2 H), 5.43 (s, 0.8 H), 6.7–7.9 (m, 19 H); mass spectrum, *m/e* 720 (M^+). Anal. Calcd for $C_{41}H_{40}N_2O_6S_2$: C, 68.31; H, 5.59; N, 3.89; S, 8.89. Found: C, 68.40; H, 5.67; N, 3.69; S, 8.87.

***N*-Benzyl-*p*-toluenesulfonanilide (18).** This compound was prepared from *p*-toluenesulfonanilide in a similar manner to that described for **12** and obtained as colorless crystals (80%), mp 139–140 °C (lit.[20] mp 133 °C).

2,5-Bis[benzyl(*p*-tolylsulfonyl)amino]toluene (19b). To a solution of 0.54 g (1.25 mmol) of **19a**[3] and 0.64 g (3.75 mmol) of benzyl bromide in 20 mL of acetone were added 0.52 g (3.75

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(18) Though we have had so far no evidence with respect to the "sense of S–N cleavage" of arenesulfonamide **12**, it seems germane, in the case of electrochemical reduction in an aprotic medium, that the electrogenerated anion radical $[ArSO_2X]^{-}\cdot$ (X = NR′R″, OR, or alkyl) dissociates to produce arenesulfinyl radical ($ArSO_2\cdot$) and anion (X^-).[9a] On the other hand, W. D. Closson et al. recently reported that the arenesulfonate esters undergo one-electron cleavage of the S–O bond on treatment with sodium–naphthalene, producing alkoxy radical and arenesulfinate anion: Closson, W. D.; Ganson, J. R.; Rhee, S. W.; Quaal, K. S. *J. Org. Chem.* **1982**, *47*, 2476. Thus, even in the case of electrochemical reduction, it may be important to consider the possibility of such a mode of cleavage.

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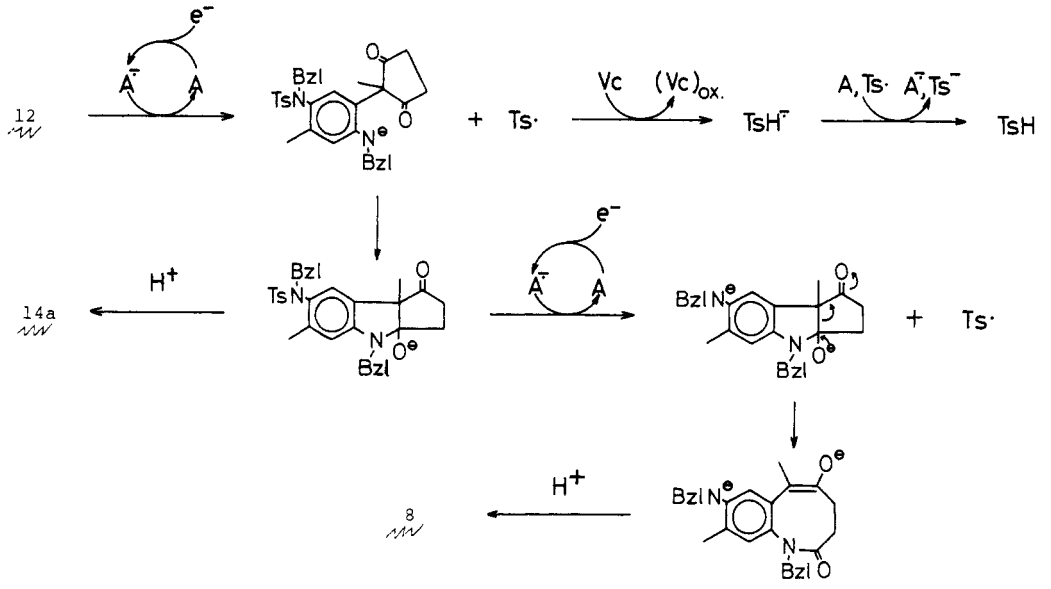
Scheme IX



mmol) of K_2CO_3 and 0.21 g (3.75 mmol) of KI, and the mixture was refluxed for 20 h. After the same workup as that described for **12**, the crude mixture was chromatographed on silica, eluting with CH_2Cl_2. Crystallization from ether gave 0.71 g (92%) of **19b** as colorless crystals: mp 188–189 °C; IR (Nujol) 1595, 1350, 1165 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.81 (s, 3 H), 2.43 (s, 6 H), 4.09 (br d, J = 13.6 Hz, 1 H), 4.62 (s, 2 H), 4.91 (br d, J = 13.6 Hz, 1 H), 6.3–6.4 (m, 1 H), 6.5–6.6 (m, 2 H), 6.9–7.6 (m, 18 H); mass spectrum, m/e 610 (M^+). Anal. Calcd for $C_{35}H_{34}N_2O_4S_2$: C, 68.82; H, 5.61; N, 4.59; S, 10.50. Found: C, 68.76; H, 5.61; N, 4.73; S, 10.53.

2-[Benzyl(*p*-tolylsulfonyl)amino]-4-(2,5-dioxo-1-methylcyclopentyl)-5-[(*p*-tolylsulfonyl)amino]toluene (20a). To a solution of 0.43 g (0.80 mmol) of **11a**[3] and 0.20 g (1.19 mmol) of benzyl bromide in 4 mL of DMF were added 0.13 g (0.96 mmol) of K_2CO_3 and 0.03 g (0.18 mmol) of KI, and the mixture was stirred for 2 days at room temperature. After cooling, the mixture was poured into ice-cold water and extracted with AcOEt. The organic layer was washed with brine, dried (Na_2SO_4), and removed under vacuum, and the residue was chromatographed on silica, eluting with CH_2Cl_2. Crytstallization from petroleum ether gave 0.48 g (95%) of **20a** as colorless crystals: mp 228–229 °C dec; IR (Nujol) 3525, 1750, 1355, 1165 cm^{-1}; ^1H NMR ($CDCl_3$–Me_2SO-d_6) δ 1.09 (s, 1 H), 1.12 (s, 2 H), 1.94 (s, 2 H), 2.00 (s, 1 H), 2.1–2.5 (m, 9 H), 3.2–3.5 (m, 1 H), 3.96 (d, J = 13.2 Hz, 0.7 H), 4.06 (d, J = 13.2 Hz, 0.3 H), 4.85 (d, J = 13.2 Hz, 0.3 H), 4.94 (d, J = 13.2 Hz, 0.7 H), 6.34 (s, 0.7 H), 6.42 (s, 0.3 H), 7.0–8.0 (m, 14 H); mass spectrum, m/e 630 (M^+). Anal. Calcd for $C_{34}H_{34}N_2O_6S_2$: C, 64.74; H, 5.43; N, 4.44; S, 10.17. Found: C, 64.64; H, 5.42; N, 4.26; S, 10.30.

General Procedure for Cyclic Voltammetry. An apparatus for electrochemical measurements consisted of three electrodes, i.e., a hanging mercury drop electrode[16] as a working electrode, a platinum plate (2 cm × 2 cm) as a counterelectrode, and a saturated calomel electrode (SCE) as a reference electrode, which was used in conjunction with a salt bridge containing saturated KCl in 2% agar gel. A platinum wire was also used as a quasi-reference electrode.[11] After nitrogen was passed through the medium for 30 min, cyclic voltammetry was measured at room temperature in 0.1 M Et_4NBF_4/DMF under nitrogen atmosphere.

Preparative Electrolysis of 12. (a) Method A (General Procedure). An apparatus consisting of three electrodes, i.e., mercury pool (4 cm^2) as a cathode, carbon rod used for a battery as an anode, and SCE as a reference electrode, was used. A platinum wire and porous cup (ϕ = 1.5 cm × 7.0 cm) were used as a quasi-reference electrode and divided cell, respectively. A controlled potential electrolysis of 72 mg (0.1 mmol) of **12** was carried out in 7 mL of DMF containing a supporting electrolyte at room temperature under argon atmosphere as shown in Table I. After electrolysis, the reaction mixture was dissolved in AcOEt and the solution was washed with brine, dried (Na_2SO_4), and removed under vacuum. The residue was chromatographed on silica, eluting with 5:1 benzene/AcOEt. Thus, the major products were separated and the structures were ascertained as follows by satisfactory elemental analyses.

4-Benzyl-7-[benzyl(*p*-tolylsulfonyl)amino]-6,8b-dimethyl-3a-hydroxy-1-oxo-1,2,3,3a,4,8b-hexahydrocyclopent[*b*]indole (14a): colorless prisms, recrystallized from ether, mp 159–160 °C dec; IR (Nujol) 3430, 1740, 1335, 1155 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.18 (s, 1.8 H), 1.19 (s, 1.2 H), 1.87 (s, 1.8 H), 1.94 (s, 1.2 H), 2.0–2.4 (m, 4 H), 2.47 (s, 1.8 H), 2.52 (s, 1.2 H), 4.04 (d, J = 13.5 Hz, 0.6 H), 4.05 (d, J = 13.5 Hz, 0.4 H), 4.27 (d, J = 16.9 Hz, 0.6 H), 4.32 (d, J = 16.9 Hz, 0.4 H), 4.59 (d, J = 16.9 Hz, 0.4 H), 4.62 (d, J = 16.9 Hz, 0.6 H), 4.95 (d, J = 13.5 Hz, 0.4 H), 5.01 (d, J = 13.5 Hz, 0.6 H), 6.02 (s, 0.6 H), 6.06 (s, 0.4 H), 6.32 (s, 0.6 H), 6.34 (s, 0.4 H), 7.2–7.7 (m, 14 H); mass spectrum, m/e 566 (M^+). Anal. Calcd for $C_{34}H_{34}N_2O_4S$: C, 72.06; H, 6.05; N, 4.94; S, 5.66. Found: C, 72.04; H, 6.08; N, 4.92; S, 5.82.

4-Benzyl-7-(benzylamino)-6,8b-dimethyl-3a-hydroxy-1-oxo-1,2,3,3a,4,8b-hexahydrocyclopent[*b*]indole (14b): light yellow crystals, recrystallized from ether, mp 145–146 °C; IR (Nujol) 3425, 1720 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.11 (s, 3 H), 1.96 (br s, 3 H), 2.0–2.4 (m, 4 H), 4.04 (br d, J = 16.9 H, 1 H), 4.24 (br s, 2 H), 4.50 (br d, J = 16.6 Hz, 1 H), 4.77 (br s, 1 H), 5.85 (br s, 1 H), 5.98 (br s, 1 H), 6.36 (br s, 1 H), 7.2–7.5 (m, 10 H); mass spectrum, m/e 412 (M^+). Anal. Calcd for $C_{27}H_{28}N_2O_2$: C, 78.61; H, 6.84; N, 6.79. Found: C, 78.63; H, 6.86; N, 6.64.

1-Benzyl-8-[benzyl(*p*-tolylsulfonyl)amino]-6,9-dimethyl-2,5-dioxo-1,2,3,4,5,6-hexahydro-1-benzazocine (15): colorless amorphous solid, hardly recrystallized; IR (film) 1710, 1660, 1350, 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.44 (d, J = 6.6 Hz, 2 H), 0.45 (d, J = 6.6 Hz, 1 H), 2.17 (s, 3 H), 2.1–2.5 (m, 6 H), 2.6–2.8 (m, 1 H), 3.08 (q, J = 6.6 Hz, 0.3 H), 3.23 (q, J = 6.6 Hz, 0.7 H), 3.92 (d, J = 12.5 Hz, 0.7 H), 4.03 (d, J = 12.9 Hz, 0.3 H), 4.14 (d, J = 13.7 Hz, 0.3 H), 4.30 (d, J = 13.7 Hz, 0.7 H), 4.99 (d, J = 12.7 Hz, 0.3 H), 5.09 (d, J = 12.9 Hz, 0.7 H), 5.61 (d, J = 13.4 Hz, 0.7 H), 5.71 (d, J = 13.4 Hz, 0.3 H), 6.19 (s, 0.7 H), 6.21 (s, 0.3 H), 7.0–7.6 (m, 15 H); mass spectrum, m/e calcd for $C_{34}H_{34}N_2O_4S$ 566.2239, found 566.2240.

1-Benzyl-8-(benzylamino)-6,9-dimethyl-2,5-dioxo-1,2,3,4,5,6-hexahydro-1-benzazocine (8): colorless prisms, recrystallized from ether, mp 161–162 °C; IR (Nujol) 3450, 1710, 1655 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 0.56 (d, J = 6.6 Hz, 3 H), 2.14 (s, 3 H), 2.0–2.3 (m, 3 H), 2.5–2.7 (m, 1 H), 3.24 (q, J = 6.8 Hz, 1 H), 4.19 (dd, J = 6.5, 15.6 Hz, 1 H), 4.33 (dd, J = 6.5, 15.6 Hz, 1 H), 4.37 (d, J = 13.7 Hz, 1 H), 5.37 (d, J = 13.7 Hz, 1 H), 5.76 (t, J = 6.5 Hz, 1 H), 6.06 (s, 1 H), 7.04 (s, 1 H), 7.1–7.4 (m, 10 H); mass spectrum, m/e 412 (M^+). Anal. Calcd for $C_{27}H_{28}N_2O_2$: C, 78.61; H, 6.84; N, 6.79. Found: C, 78.44; H, 6.94; N, 6.78.

(b) Method B. A mixture of 3.60 g (5 mmol) of **12**, 0.89 g (5 mmol) of anthracene, and 1.76 g (10 mmol) of ascorbic acid was reduced in 700 mL of DMF containing 0.057 M Et_4NBF_4 at −1.7

to -1.9 V vs. SCE. A mercury pool (130 cm^2) and ultrafine fritted glass were used as a cathode and divided cell, respectively. After the electrolysis was completed (7.5 h, 6.6 F/mol), the reaction mixture was concentrated under vacuum and treated with a usual workup (method A) to give 1.73 g (84%) of **8** as a sole product.

(c) Method C. Electrolysis of 72 mg (0.1 mmol) of **12** was carried out in a mixture of 5 mL of MeOH and 5 mL of DMF containing 0.04 M Et_4NBF_4 for 1 h (11.2 F/mol) at -1.7 V vs. Pt wire. A lead plate (3 cm × 4 cm) and porous cup were used as a cathode and divided cell, respectively. The excess MeOH was removed under vacuum and the residue was treated with a usual workup (method A) and finally chromatographed on silica, eluting with 30:1 CH_2Cl_2/AcOEt, to afford 8 mg (14%) of **14a** and 30 mg (40%) of 2,5-bis[benzyl(*p*-tolylsulfonyl)amino]-4-(1-methyl-2-oxo-4-carbomethoxybutyl)toluene (**17a**) as a colorless solid. Recrystallization of this solid from ether afforded an analytical sample as colorless crystals: mp 107-108 °C; IR (Nujol) 1730, 1710, 1350, 1165 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.24 (d, J = 6.8 Hz, 2 H), 1.1-1.3 (m, 1 H), 1.80 (s, 1.5 H), 1.87 (br t, J = 4.9 Hz, 1.5 H), 2.0-2.9 (m, 10 H), 3.6-3.7 (m, 3 H), 3.8-4.2 (m, 3 H), 4.9-5.2 (m, 2 H), 6.0-6.3 (m, 1 H), 6.4-6.6 (m, 1 H), 6.9-7.8 (m, 18 H); mass spectrum, m/e 721 (M^+ - MeO). Anal. Calcd for $C_{42}H_{44}N_2O_7S_2$: C, 67.00; H, 5.89; N, 3.72; S, 8.52. Found: C, 67.30; H, 6.04; N, 3.77; S, 8.75.

(d) Method D. Electrolysis of 72 mg (0.1 mmol) of **12** was carried out in a mixture of 5 mL of EtOH and 5 mL of DMF containing 0.04 M Et_4NOTs for 7 min (1.2 F/mol) at -1.7 V vs. Pt wire. After the same workup as that described for method C, 3 mg (5%) of **14a** and 48 mg (63%) of 2,5-bis[benzyl(*p*-tolylsulfonyl)amino]-4-(1-methyl-2-oxo-4-carboethoxybutyl)-toluene (**17b**) as a colorless solid were obtained. Recrystallization of this solid from ether afforded an analytical sample as colorless crystals: mp 108-110 °C; IR (Nujol) 1725, 1710, 1350, 1165 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.24 (d, J = 6.8 Hz, 2 H), 1.21 (t, J = 7.3 Hz, 3 H), 1.1-1.3 (m, 1 H), 1.80 (s, 1.5 H), 1.87 (br t, J = 4.6 Hz, 1.5 H), 2.0-2.9 (m, 10 H), 4.09 (q, J = 7.3 Hz, 2 H), 3.8-4.2 (m, 3 H), 4.9-5.2 (m, 2 H), 6.0-6.3 (m, 1 H), 6.4-6.6 (m, 1 H), 6.9-7.8 (m, 18 H); mass spectrum m/e 766 (M^+). Anal. Calcd for $C_{43}H_{46}N_2O_7S_2$: C, 67.34; H, 6.05; N, 3.65; S, 8.36. Found: C, 67.51; H, 6.01; N, 3.46; S, 8.32.

Photolysis of 12. A mixture of 1.44 g (2.0 mmol) of **12**, 0.78 g (4.4 mmol) of ascorbic acid, and 0.38 g (2.0 mmol) of 1,5-dimethoxynaphthalene was irradiated with a 500-W, high-pressure mercury lamp through a Pyrex filter in 80% aqueous THF for 8 h under argon atmosphere. The reaction mixture was then neutralized with saturated aqueous $NaHCO_3$ and the solvent was removed under vacuum. The residue was dissolved in AcOEt, and the solution was washed with brine, dried (Na_2SO_4), and evaporated to give the crude mixture. After chromatography on silica, eluting with 5:1 benzene/AcOEt, 0.40 g (48%) of **14b** was obtained as the sole product.

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Registry No. **8**, 88609-66-9; **9c**, 14818-63-4; **10c**, 88589-44-0; **11a**, 72374-10-8; **11b**, 88589-45-1; **12**, 88589-36-0; **14a**, 88589-37-1; **14b**, 88589-38-2; **15**, 88589-39-3; **17a**, 88589-40-6; **17b**, 88589-41-7; **18**, 4703-20-2; **19a**, 72374-00-6; **19b**, 88589-42-8; **19c**, 72374-01-7; **20a**, 88589-43-9; **20b**, 72374-11-9; benzyl bromide, 100-39-0; *p*-toluenesulfonanilide, 68-34-8; anthracene, 120-12-7; ascorbic acid, 50-81-7.

Substituent Electronegativity Parameters

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Values are reported of the atomic electron population on the hydrogen atom in compounds HX as calculated at the ab initio molecular orbital 6-31G* level with geometry optimization. It is shown that these provide a simple and well-defined scale of electronegativity parameters. It is further shown that the one-bond J_{CC} values for C1C2 in monosubstituted benzenes for many but not all substituents are a function of substituent electronegativity.

The concept of electronegativity has been said[1] to be "simultaneously one of the most important and one of the most difficult problems in chemistry". Another recent comment[2] is that "few concepts are as widely used, or as ambiguous ... this situation may be attributed to the fact that the electronegativity of an atom, or functional group, is neither uniquely defined nor directly measurable".

Pauling[3] originally defined electronegativity as "the power of an atom in a molecule to attract electrons to itself". Pauling determined his scale from thermochemical data, but difficulties here have led[4] to alternative bases becoming more common. One approach[1,5-7] is to calculate valence state or orbital electronegativities by using a combination of ground-state ionization energies and electron affinities, together with calculated or spectroscopically determined transition energies. An alternative approach[1,5,8,9] is to consider electronegativity to be some function of the size and charge of an atom, for example, by using covalent boundary potentials. Various refinements have been made to these approaches, but electronegativity scales remain empirical although recently[2] values have been calculated for the first 54 elements on the basis of the electrostatic force between the effective nuclear

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